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Serial No.: 09/974,519

REMARKS

Status Summary

Claims 1-27 in the present U.S. patent application as filed were subject to a Restriction/Election Requirement. Claims 1-16 were elected for prosecution. Claims 17-27 have been withdrawn from consideration.

Applicants were further required to elect species upon which a search could be initiated. Applicants elected the following species: (a) the phospholipase C inhibitor as an alkylphosphocholine; (b) the form of administration as oral administration; (c) a method as recited in claim 1, a method of enhancing paracellular permeability; and (d) the absorption site comprising intestinal epithelium as recited in claim 6. It appears the Examiner limited searching to only these species, and therefore claims 1-3 and 8 are currently under examination. Applicants note that claim 6 should also have been included within the claims searched that encompass the elected species, as claim 6 recites the absorption site comprising intestinal epithelium. It is presumed this was an oversight and that claims 1-3, 6 and 8 are currently under examination. Applicants remarks are therefore inclusive of claims 1-3, 6 and 8.

Reconsideration of the application based on the arguments set forth below is respectfully requested.

Claim Rejection - 35 U.S.C. § 103(a)

Claims 1-3 and 8 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over the journal article to Liu et al. (Liu et al., *J. Pharm. Sci.* 88(11): 1161-1168 (1999), hereinafter, "Liu et al.") in view of U.S. Patent No. 5,144,045 to Wissner et al. (hereinafter, "Wissner '045"). This rejection is respectfully traversed.

The Examiner contends Liu et al. teach "an alkyl phosphocholine for enhancement of Para cellular permeability to overcome the barrier to absorption

of orally administered hydrophilic drugs posed by tight junctions in the intestinal epithelium." Official Action at p. 2. The Examiner further contends that Wissner '045 teach "orally administered phosphocholine derivatives for inhibition of a phospholipase." Official Action at p. 2. The Examiner argues that it would have been obvious to one of skill in the art to "deliver the treatment of Liu et al. by oral administration in view of the teaching of Wissner et al '045 that such administration is efficacious for inhibition of a phospholipase." Official Action at p. 3. Applicants respectfully traverse the Examiner on the grounds of this rejection.

Claims 2, 3, 6 and 8 depend from claim 1. Therefore, claims 2, 3, 6 and 8 include the elements of claim 1. Claim 1 recites a method of enhancing paracellular permeability at an absorption site in a subject. The method comprises administering an effective amount of a phospholipase C inhibitor to a subject at a time in which enhanced paracellular permeability is desired, and enhancing paracellular permeability in the subject at the absorption site through the administering of the effective amount of the phospholipase C inhibitor. Applicants respectfully submit that neither Liu et al. nor Wissner '045 teach or suggest enhancing paracellular permeability at an absorption site by administering an effective amount of a phospholipase C inhibitor. Additionally, neither Liu et al. nor Wissner '045 offer a suggestion to modify the methods disclosed therein to arrive at the above step and, consequently, the method proposed by the Examiner would not be obvious to one of ordinary skill in the art.

Specifically, Liu et al. teach that dodecylphosphocholine (DPC) can improve paracellular permeability across Caco-2 cell monolayers. Liu et al. recognize that numerous classes of compounds act in a variety of known (e.g. as detergents or Ca^{2+} chelators) and unknown ways. See Liu et al. at p. 1161, col. 2. However, Liu et al. report that although DPC can improve paracellular permeability, the mechanism of action of the improvement by DPC is unknown.

See Liu et al. at p. 1166 col. 1 and 2. Therefore, since Liu et al. do not have an understanding of the mechanism of action of enhancement of paracellular permeability, Liu et al. cannot teach or suggest enhancing paracellular permeability by inhibition of the biological activity of the enzyme phospholipase C through the administration of a phospholipase C inhibitor, as recited in claim 1.

Wissner '045 also do not teach or suggest enhancing paracellular permeability at an absorption site by administering an effective amount of a phospholipase C inhibitor. Wissner '045 only teach compounds for the inhibition of a phospholipase A_2 enzyme. Phospholipase A_2 and phospholipase C are unrelated in cellular location, cellular regulation, and substrate specificity. Phospholipase A_2 hydrolyzes acyl groups attached to the C_2 of a phosphoglyceride. It is rich in pancreatic solutions and requires bile acids for activity. Wissner '045 teach that phospholipase A_2 is also involved in the production of platelet activating factor, leukotrienes and prostacyclin and as such is indirectly involved with the inflammatory response. See Wissner '045 at col. 1, lines 12-30. In contrast, phospholipase C hydrolyzes the phosphate linkage of phosphotidyl inositol bisphosphate to produce inositol triphosphate and diacyl glycerol, which serve as second messengers in cell signaling pathways.

Wissner '045 teach that the compounds disclosed therein are useful in the treatment of a disorder that "results from the direct action of phospholipase A_2 or the mediators produced as a result of its activity." Wissner '045 at col. 4, lines 36-40. Nowhere does Wissner '045 teach or suggest that the compounds disclosed therein would also be effective at inhibiting phospholipase C, nor does Wissner '045 teach or suggest that inhibiting phospholipase C will enhance paracellular permeability at an absorption site.

Applicants urge that the cited references, Liu et al. and Wissner '045, cannot be combined to ith r t ach or suggest each and every element of the

presently claimed subject matter and therefore that claims 1-3, 6 and 8 are not obvious in view of the cited references. Applicants therefore respectfully request that the rejection of claims 1-3, 6 and 8 under 35 U.S.C. §103(a) based on these documents be withdrawn and that the claims allowed at this time.

In the alternative, even assuming arguendo that the combination of Liu et al. with Wissner '045 disclose each and every element of the claimed invention as the Examiner contends, applicants submit that the cited references offer no explicit or implicit suggestion to combine the cited references. Applicants submit that at best, the cited references are simply an "invitation to experiment" and present an "obvious-to-try" situation. An "obvious-to- try" situation is held to exist

> when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.

In re Eli Lilly & Co., 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990).

Courts have painstakingly distinguished between obviousness under 35 U.S.C. §103 and an "obvious-to-try" situation. "[W]e have consistently held that 'obvious-to-try' is not to be equated with obviousness under 35 U.S.C. §103." The Gillette Co. v. S.C. Johnson & Son, Inc., 16 U.S.P.Q.2d 1923, 1928 (Fed. Cir. 1990).

Liu et al. report that although DPC can improve paracellular activity across Caco-2 monolayers, the mechanism of action is unknown. As previously discussed, since Liu et al. do not have an understanding of the mechanism of action of enhancement of paracellular permeability, Liu et al. cannot teach or suggest enhancing paracellular permeability by inhibition of the biological activity of the enzyme phospholipase C through the administration of a phospholipase C inhibitor, as recited in claim 1. Wissner '045 only teach compounds for the inhibition of a phospholipase A_2 nzyme, not a

phospholipase C enzyme. As previously discussed, phospholipase A_2 and phospholipase C are completely unrelated in cellular location, cellular regulation, and substrate specificity. Therefore, there is no motivation for one of skill in the art to modify the teachings of Liu et al. with those of Wissner '045. Applicants respectfully submit that the cited references alone or in combination present at best an "obvious-to-try" situation and lack both a suggestion to modify the references to arrive at the presently claimed subject matter, and the necessary elements to practice the presently claimed subject matter with a reasonable expectation of success even if the references are combined as proposed by the Examiner.

Summarily, applicants respectfully submit that the Patent Office has not presented a prima facie case of obviousness. As such, applicants further submit that independent claim 1 and dependent claims 2, 3, 6 and 8 are in condition for allowance and respectfully request that the rejection of claims 1-3, 6 and 8 under U.S.C. §103(a) be withdrawn and that the claims be allowed at this time.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

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DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

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